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Intracerebral haemorrhage

J M MacKenzie

Spontaneous (that is, non-traumatic) intracerebral haemorrhage (ICH) is a common problem and, with subarachnoid haemorrhage, accounts for 15% of all strokes.[1] The annual incidence is 15–30/100 000.[2 3]

The mortality rate is high with an overall 28 day mortality of 35% in one study[3] and a 30 day mortality of 44% in another.[2] However, the mortality rate is closely correlated with size and site of haematoma, and the Glasgow Coma Scale (GCS) score at presentation. The 30 day mortality for patients with a haematoma larger than 60 cm^3 and GCS score of 8 or less is 91%, whereas the 30 day mortality for those with a volume of less than 30 cm^3 and a GCS score of 9 or more is only 19%.[2] The site is also important—brainstem haematomas are 100% fatal at 28 days, whereas the mortality for basal ganglia or thalamic haematomas is 22%.[3]

Hypertension is still the main cause, being responsible for approximately 55% of cases of spontaneous ICH, although the association is stronger for some sites than for others—for example, 67% of patients with lobar haemorrhages have a history of hypertension, as do 78% of those with pontine haemorrhages.[4 5] However, there are a number of other important causes such as vascular malformations, drug abuse and amyloid angiopathy, the last being particularly important as a cause of lobar haemorrhages, often multiple, in non-hypertensive, elderly patients.[6 7]

Once an intracerebral haematoma has formed, a series of pathophysiological events is initiated, including the development of cerebral oedema and an ischaemic penumbra in which excitotoxic neuronal injury occurs.[1 8]

This article discusses, firstly, the pathophysiology of ICH, secondly, some of the more important aetiologies of ICH, and, thirdly, the pathological investigation of cases of ICH.

Pathophysiology of spontaneous intracerebral haemorrhage

Irrespective of the underlying aetiology of ICH, once a haematoma has formed within the brain, a number of pathophysiological events occur. Most haematomas result from rupture of an artery or arteriole and, therefore, the haematoma is formed at, or near to, arterial pressure.[1] In this context the effects of disruption of the cerebral tissue by the haematoma are easy to understand and vary depending on the anatomical location of the haematoma. The effects of raised intracranial pressure often ensue and lead to death: midline shift with distortion and down thrust of the diencephalon resulting in disorders of consciousness; transtentorial herniation of medial temporal structures with compression of the ipsilateral oculomotor nerve and posterior cerebral/posterior communicating arteries; secondary brainstem haemorrhage; and cerebellar tonsillar herniation with medullary compression. Fatality may occur in association with any of these events.

In 14% of cases spontaneous intracerebral haemorrhage is not a monophasic event, and expansion may occur, usually within the first six hours after onset. Expansion is associated with liver dysfunction, coagulation abnormalities and irregularity of haematoma contours on the original scan and also with poor clinical outcome.[9]

It has been recognised that a haematoma is surrounded by an ischaemic penumbra which may be larger than the haematoma itself.[1 10] The ischaemia is due partly to direct mechanical compression and also to the release of vasoactive substances from extravasated blood—factors which might also play a role in the development of oedema within the surrounding tissue, so exacerbating the space-occupying effects of the haematoma.[8] Within the ischaemic penumbra a number of dynamic processes take place which eventually lead, if uninhibited, to irreversible neuronal injury. Waves of depolarisation, extracellular increases in excitatory amino acids, activation of calcium channels, induction of immediate early genes such as c-*fos* and c-*jun* and expression of heat-shock proteins all play a role in mediating tissue damage, but the precise relation among these factors remains obscure.[11] The process of tissue damage in the ischaemic penumbra is time dependent and it is possible that re-establishment of perfusion through this zone three to four hours after the initial insult may prevent lethal injury.[12] However, there is uncertainty about the benefits of both surgical evacuation of haematomas,[13] and cytoprotection in the ischaemic penumbra using—for example, glutamate receptor antagonists and sodium channel blockers, clinical trials of which have been disappointing. In animal models the "therapeutic window" is less than two hours[14] so while there is theoretical scope for therapeutic intervention in ICH, the opportunity is limited and the potential for benefit uncertain.

Although the mortality rate for ICH is high, not all patients die in the early stages, and the natural history of non-fatal, unevacuated haematomas is their gradual attenuation, as blood elements are degraded and removed by phagocytes and the haematoma becomes surrounded by connective tissue.[15] Haemorrhage, like an abscess, is a potent stimulus to fibrosis within the brain, and the end result is either a haemosiderin stained scar or a cavity containing old blood surrounded by fibrous tissue.

Department of Pathology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZD

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A recently defined clinicopathological entity has been termed "encapsulated intracerebral haematoma". This presents as an intracranial space-occupying lesion, often in young, normotensive patients. Approximately half of the cases are associated with a proven vascular malformation.[16] This is an important differential diagnosis for a ring-enhancing intracerebral space-occupying lesion on computed tomography or magnetic resonance (MR) scanning, as it may mimic, clinically and radiologically, a malignant glioma. Histologically, the diagnosis is simple, as the lesion consists of blood clot and gliofibrotic granulation tissue, although caution is necessary in differentiating this lesion from a glioma complicated by haemorrhage, which is a frequent occurrence.

Aetiology of spontaneous intracerebral haemorrhage

HYPERTENSION

Despite the better control of hypertension, which has contributed significantly to the declining incidence of stroke,[17] it remains the commonest cause of spontaneous ICH. In a recent study of 163 cases of ICH, 118 (72%) had clinical and/or electrocardiographic evidence of hypertension, and most of the haematomas were present in deep cerebral structures (47%), or were lobar—that is, involving only cortical and subcortical areas (40%).[5]

Despite the strong association between ICH and hypertension, the pathological processes linking the two remain unclear. It is still widely believed that hypertensive ICH is due to rupture of "microaneurysms", both in general pathology[18] and neuropathology texts,[19] largely based on the original work of Charcot and Bouchard and subsequent studies of Cole and Yates.[20] Recent studies eliminating injection artefacts have cast considerable doubt on the frequency of such microaneurysms and their supposed relation to ICH, suggesting that many of the structures previously described in hypertensive brains as "microaneurysms" are, in fact, complex vascular coils.[21 22] However, if most of these structures are vascular tortuosities, rather than "microaneurysms", the cause of ICH in hypertension remains elusive, although one possible explanation is fibrinoid necrosis of small arteries and arterioles.[23]

RUPTURED SACCULAR ANEURYSMS

These are a frequent cause of spontaneous ICH or intraventricular haemorrhage, particularly in patients dying within the first week.[24] Middle cerebral artery aneurysms in the Sylvian fissures may produce a pattern of ICH similar to a deep hypertensive ICH, whereas anterior communicating aneurysms tend to rupture into the anterior horns of the lateral ventricles, so producing intraventricular haemorrhage. ICH from a ruptured aneurysm always has a subarachnoid component, but this is rarely the case with haemorrhages of other aetiologies, except where the haemorrhage is cortical or subcortical in location—a frequent occurrence in cerebral amyloid angiopathy.[6]

CEREBRAL AMYLOID ANGIOPATHY

It has been claimed that cerebral amyloid angiopathy (CAA) is the commonest cause of ICH in patients over 65 years of age[25] but the evidence suggests that hypertension remains the commonest cause in this age group.[5] Nevertheless, CAA is an important cause of ICH, typically causing multiple subcortical haemorrhages which, because of the location, may involve the subarachnoid space, although rarely being a cause of primary subarachnoid haemorrhage.[26] Over 40% of patients with CAA are demented and most show the presence of neuritic plaques and neurofibrillary tangles at necropsy.[6 7] The blood vessels most frequently affected are small to medium sized vessels (30–250 μm in diameter) in the cerebral cortex.[7] β amyloid, with a chemical structure closely homologous to that of the amyloid of Alzheimer's disease and Down's syndrome, replaces smooth muscle cells of the vascular tunica media, producing separation of the internal elastic lamina and the vascular basement membrane.[6] Severe amyloid deposition in vessels over 200 μm seems particularly closely associated with subcortical haemorrhage in CAA[27] and many of the amyloid laden vessels in patients with ICH show the presence of fibrinoid necrosis, with or without "microaneurysms" on small cortical arteries 40–50 μm in diameter.[28 29] However, the role of hypertension in producing some of these changes is not clear. It is known that more than 30% of individuals with CAA related ICH have clinically documented hypertension, and hypertension may exacerbate the tendency to CAA related haemorrhage.[6]

VASCULAR MALFORMATIONS

Arteriovenous malformations

Arteriovenous malformations (AVMs) are an important cause of spontaneous intracranial haemorrhage, which may recur unpredictably with major rebleeding and mortality rates of 4% and 1% per annum, respectively.[30 31] Most AVMs arise on the surface of the cerebrum in the middle cerebral territories and consist of abnormal vessels of varying size and mural architecture, often separated by septa of gliotic, haemosiderinised brain. "Arterialised veins"—veins showing muscular hyperplasia and fibrosis as a response to perfusion at abnormally high pressures—are particularly characteristic. The lesions are in the nature of arteriovenous shunts through abnormal blood vessels and such shunting is seen clearly on angiography.[32] Aneurysms may also arise on the component vessels of an AVM and constitute a source of haemorrhage.[30]

Cavernous angiomas

Although less likely than AVMs to present with catastrophic ICH, cavernous angiomas are, nevertheless, important vascular lesions which may be the most common vascular malformation encountered in children. Most lesions show evidence of occult bleeding on MR scanning or histological examination, but only

9–12% have clinically significant haemorrhage with an annualised bleeding rate of 0·7%.[33 34] They present clinically with seizures, sudden onset of neurological deficit and headache, or slowly progressive neurological deficits.[35] Cavernous angiomas tend to be angiographically invisible, although readily identifiable on MR scanning as a cortical mass of abnormal vessels surrounded by cerebral parenchyma containing abundant haemosiderin.[36] Microscopically, cavernous angiomas consist of vessels with collagenous walls devoid of muscle and elastic tissue. Areas of scarring, recent or old haemorrhage and calcification are present in most lesions and foci of glial tissue may be entrapped between the vessels.[32 35]

Venous angiomas

These consist of radially arranged, anomalous medullary veins which converge on a dilatated central draining vein, the vessels being surrounded by normal brain tissue.[37] It has been argued that these malformations represent anomalous venous drainage and occur mostly as incidental findings in patients investigated for neurological symptoms and signs with some alternative causation.[37 38] Haemorrhage is considered rare and on this basis, it has been stated that surgical resection of the lesion is rarely warranted.[39] Even the relatively low risks of radiosurgery seem to outweigh the benefits in a lesion with such a benign natural history.[40] However, this view is not universally accepted, and in some studies, the incidence of clinically significant intracranial haemorrhage has been as high as 43%, leading to the suggestion that surgical extirpation should be considered in all cases in which a venous angioma is associated with haemorrhage.[41]

Capillary telangiectasias

These are usually incidental findings at necropsy, but they may occasionally be symptomatic if located in the brain stem or spinal cord. Bleeding is very rare. They consist of small vessels without smooth muscle and containing little collagen, randomly distributed in normal brain parenchyma.[32]

IATROGENIC FORMS OF ICH

Iatrogenic forms of ICH may be divided into two categories: (1) those due to self administration of substances with toxic effects; and (2) those due to therapeutic manipulations. The most important substances in the first category are alcohol, cocaine and amphetamines. There is clear evidence that heavy alcohol consumption predisposes to spontaneous ICH.[42] There are a number of mechanisms by which heavy alcohol consumption may predispose to ICH, the foremost of which are the induction of hypertension, particularly acutely after a binge, or its inhibiting effects on platelet function.[3] Furthermore, liver dysfunction associated with chronic alcohol consumption is a significant risk factor for haematoma enlargement in ICH,[9] and the incidence of liver dysfunction and alcohol consumption is higher in patients with ICH than with subarachnoid haemorrhage.

Cocaine is known to be associated with ICH, particularly when snorted or smoked as "crack". In most cases, this has been associated with an underlying vascular lesion such as an aneurysm or an AVM, and it seems likely that the pathogenesis is transient hypertension secondary to cocaine induced blockage of noradrenaline uptake and consequent sympathetic hyperactivity.[44 45] There is also some evidence that cocaine induces a cerebral vasculitis, which may be partly responsible for ICH associated with use of cocaine.[46] Amphetamines are associated with ICH and it seems likely that the mechanisms are similar to those underlying the association between cocaine and ICH.[47 48]

Numerous forms of ICH secondary to therapeutic manipulations have been described. Serious bleeding requiring hospitalisation occurs yearly in 1–4% of elderly patients on warfarin within the International Normalised Ratio (INR) range of 2–4 for cerebrovascular disease or atrial fibrillation, although the risk seems less in patients under 75 years of age.[49] In our experience fatal ICH in patients undergoing long term anticoagulation is associated with poor control of anticoagulation and INR values greater than 5, and this is supported by case control studies.[50] There is a risk of haemorrhagic transformation or development of ICH in patients treated with tissue plasminogen activator (TPA) for ischaemic stroke. The risk is unclear with some studies showing no difference between treated and control groups,[51] while others claim an 11% risk of ICH at 24 hours after symptom onset in patients treated with TPA.[52] There is also a risk of ICH following fibrinolytic therapy after acute myocardial infarction.[53] ICH may complicate carotid endarterectomy for symptomatic carotid atherosclerosis in around 2% of cases and is associated with high blood flow velocity following de-clamping of the artery as assessed by transcranial Doppler monitoring.[54]

OTHER CAUSES OF ICH

These are numerous and diverse, including: pre-eclampsia[55]; haemorrhagic transformation of an ischaemic infarct in infective endocarditis[56]; placement of a ferromagnetic clip in a magnetic field[57]; cerebral artery dissection[58]; and as a delayed complication of angiospasm following aneurysm rupture.[59] Bleeding into primary or metastatic tumours is also an important cause of ICH and such tumours do occasionally present as a stroke. The causes presented in this paper are not intended to be all encompassing. The intention is simply to define some of the more important conditions associated with ICH.

Pathological investigation of spontaneous intracerebral haemorrhage

In necropsy cases the clinician is usually interested in finding out what caused the haemorrhage, what caused death and whether or not

there were any preventable complications. A thorough study of the case notes and discussion with the clinician to clarify any points of difficulty is an essential preparatory step. Examining the radiological preparations will also provide useful information about the site and size of the haematoma. The general necropsy should identify evidence of hypertension or any other factor, such as a coagulopathy, which may be associated with ICH. Detailed examination of the brain should be deferred until adequate fixation has taken place—at least two months if a large intracerebral clot is present—but much information can be gained from an external examination. The presence of generalised subarachnoid blood should prompt a search for an aneurysm or arteriovenous malformation, both of which are easily seen externally, and the presence of blood in the posterior fossa in the absence of an aneurysm should prompt consideration of vertebral artery rupture.[60] The site, size and number of haemorrhages, together with any other relevant features should be noted on the fixed brain slices. Careful attention should be directed to the surrounding brain tissue—an AVM or tumour may be identified.

Microscopic examination of surgically evacuated or necropsy clots and the surrounding brain is not a useless exercise. The commonest entity to be identified only at the microscopic level is amyloid angiopathy, and it is unusual for a vascular malformation or tumour to be identified only microscopically, although this does sometimes occur. Evidence of vasculitis should be treated with caution, unless present remote from the haematoma, as a variety of reactive vascular changes swiftly ensue in the immediate vicinity of the haematoma.

Contrary to what is commonly supposed, it is possible to identify the aetiology of spontaneous ICH in most cases. A case should only be labelled as "hypertensive ICH" if there is clear evidence of hypertension: a clinical history of hypertension on treatment; ECG evidence of left ventricular hypertrophy; pathological evidence of the same as assessed by the left ventricular weight[61]; evidence of hypertensive changes in the brain and other organs. If there is no evidence of the patient having been hypertensive and no other definite cause, the designation "spontaneous ICH of unknown aetiology" is more appropriate.

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